

14. The method of claim 13, wherein said detecting identifies a ligand variant having optimal binding activity to said one or more receptors.

15. The method of claim 10, wherein said
5 ligand variant population is recombinantly expressed in cells.

16. The method of claim 15, wherein said cells are melanophores.

17. The method of claim 10, further comprising
10 isolating an individual ligand variant having binding activity to said one or more ligands, wherein said ligand variant is linked to an identifiable tag.

18. The method of claim 10, further comprising
15 dividing said collective ligand variant population into two or more subpopulations, contacting said two or more subpopulations with said one or more receptors and detecting one or more ligand variant subpopulations having binding activity to said one or more receptors.

19. A method for determining binding of a
20 ligand to a receptor or a variant thereof, comprising contacting a collective ligand population with said receptor or variant thereof and detecting binding of said receptor or variant thereof to said collective ligand population.

20. The method of claim 19, further comprising
25 dividing said collective ligand population into two or more subpopulations, contacting one or more of said two or more subpopulations with said receptor or variant thereof and detecting one or more ligand subpopulations

093346 042001

having binding activity to said receptor or variant thereof.

21. The method of claim 20, wherein said dividing, contacting and detecting are repeated one or
5 more times.

22. The method of claim 21, wherein said detecting identifies a ligand variant having binding activity to said receptor or variant thereof.

23. The method of claim 22, wherein said
10 detecting identifies a ligand variant having optimal binding activity to said receptor or variant thereof.

24. The method of claim 19, wherein said collective ligand population contains ligand variants.

25. The method of claim 19, further comprising
15 dividing said collective ligand population into two or more subpopulations, contacting said two or more subpopulations with said receptor or variant thereof and detecting one or more ligand subpopulations having binding activity to said receptor or variant thereof.

20 26. A method for identifying an optimal binding ligand variant for a receptor, comprising:

(a) contacting a collective receptor variant population or subpopulation thereof with a ligand population;

25 (b) detecting binding of one or more ligands in said ligand population to said collective receptor variant population or subpopulation thereof;

093466 04001
"00240" 5945360

(c) dividing said ligand population into subpopulations; and

(d) repeating optionally each of steps (a) to (c), wherein said ligand subpopulation in step (c) comprises two or more ligands and is used as said ligand population in step (a) and wherein said detecting in step (b) identifies one or more ligands having binding activity to said collective receptor variant population.

27. The method of claim 26, further comprising the steps:

(e) generating a library of variants of said ligand identified in step (d);

(f) contacting a parent receptor with each of said ligand variants; and

(g) detecting the binding of one or more ligand variants to said parent receptor.

28. The method of claim 26, wherein step (d) further comprises comparing the binding activity of said one or more ligands having binding activity to said receptor variant population.

29. The method of claim 28, wherein said comparing identifies a ligand having optimal binding activity to said collective receptor variant population.

30. The method of claim 27, wherein said step (g) further comprises comparing the binding activity of said one or more ligand variants having binding activity to said parent receptor.

093946-04201

31. The method of claim 30, wherein said comparing identifies a ligand having optimal binding activity to said parent receptor.

32. A method for identifying an optimal
5 binding ligand variant to a receptor, comprising:

(a) contacting two or more subpopulations of a collective receptor variant population with individual ligands from a ligand population;

(b) detecting binding of one or more
10 individual ligands to one or more of said subpopulations of said collective receptor variant population;

(c) dividing at least one of said subpopulations of said collective receptor population which exhibits binding activity to said individual
15 ligands into two or more new subpopulations; and

(d) repeating optionally each of steps (a) to (c), said two or more new subpopulations in step (c) comprising two or more receptor variants and said new subpopulations used as said two or more subpopulations of
20 a collective receptor variant population in step (a), wherein said detecting in step (b) identifies one or more individual ligands having binding activity to one or more new subpopulations of subpopulations of said collective receptor variant population.

25 33. The method of claim 32, further comprising the steps:

(e) contacting a closely related receptor variant subpopulation comprising a parent receptor or a

0533465-042001
TOP SECRET 69463350

closely related variant thereof with one or more individual ligands identified in step (d);

(f) detecting binding of said one or more individual ligands to said closely related receptor variant subpopulation; and

(g) comparing the binding activity of said one or more ligands having binding activity to said closely related receptor variant subpopulation, wherein said comparing identifies a ligand having optimal binding activity to said closely related receptor variant subpopulation.

34. The method of claim 33, further comprising the steps:

(h) generating a library of variants of said ligand identified in step (g);

(I) contacting said parent receptor with each of said ligand variants; and

(j) detecting binding of one or more ligand variants to said parent receptor.

35. The method of claim 32, wherein step (d) further comprises comparing the binding activity of said one or more ligands having binding activity to said closely related receptor variant population.

36. The method of claim 35, wherein said comparing identifies a ligand having optimal binding activity to said collective receptor variant population.

37. The method of claim 34, wherein said step (j) further comprises comparing the binding activity of said one or more ligand variants having binding activity to said parent receptor.

5 38. The method of claim 37, wherein said comparing identifies a ligand having optimal binding activity to said parent receptor.

093946 042001